UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/825,257	04/14/2004	Lindsay H. Burns	14938US02	8108

24573 7590 12/21/2007
BELL, BOYD & LLOYD, LLP
P.O. Box 1135
CHICAGO, IL 60690

EXAMINER
CLAYTOR, DEIRDRE RENEE

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
12/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/825,257	BURNS ET AL.	
	Examiner	Art Unit	
	Renee Claytor	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-39 and 41-272* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 5,7,11-13,15-21,55-71,75,76,78,79,81,82,84-86,88-95,104,105,107-110,128,129,131,132,134-140,142,152,154-157 and 174-272.

Continuation of Disposition of Claims: Claims rejected are 1,4,6,8-10,14,22-39,41-54,72-74,77,80,83,87,96-103,106,111-127,130,133,141,143-151,153 and 158-173.

DETAILED ACTION

Applicant's response filed on 10/10/2007 is acknowledged. Applicants point out that claims 1-272 were pending at the time of the previous Office Action which was not indicated on the PTO-326 form. The Examiner notes this and recognizes that at the time of this action, claims 1, 4-39 and 41-272 are pending with claims 1,4, 6, 8-10, 14, 22-39, 41-54, 72-74, 77, 80, 83, 87, 96-103, 106, 111-127, 130, 133, 141, 143-151, 153, 158-173 currently under examination.

Response to Arguments

Applicants have cancelled claims 3 and 40, which is sufficient to overcome the 35 USC 112, second paragraph rejections over those claims and the rejection is hereby withdrawn over those claims. Applicant's further amended claim 4 to remove the limitation of "the excitatory opioid receptor antagonist" that was previously in the claim. This amendment is sufficient to overcome the 35 USC 112, second paragraph rejection over claim 4 and the rejection is hereby withdrawn.

Applicants argue that the 35 USC 112, first paragraph rejection is improper because the specification enables the claimed invention of using opioid antagonists to treat any type of neuropathic pain. Due to Applicants amendments to the claims, by adding the limitation of an opioid agonist and the knowledge skill of those in the art, the 35 USC 112, first paragraph rejection is hereby withdrawn.

Applicants have amended claim 1 to recite that the composition additionally comprises an opioid agonist and argue that the 35 USC 102 rejection as being

anticipated by Levine should be withdrawn because the composition of Levine only comprises an opioid antagonist. The Examiner does not agree with this assertion because Levine teaches administering an opioid agonist and antagonist. Because claim 1 has been amended to include a combination of an opioid antagonist and agonist, this is being addressed in the modified rejection given below.

Applicants argue over the references of the 35 USC 103 rejection and first argue that the portion of the Mitch reference relied upon refers to opioid agonist-antagonists and that nowhere in the application is the amount of the antagonist that is effective to enhance the pain-alleviating potency of the administered agonist described and that it would not be obvious to use an opioid antagonist to enhance the pain alleviating effects of an opioid agonist because an antagonist would be presumed to reduce the pain alleviating effect of the agonist, not enhance it. In response to the above arguments, it is noted that Mitch teaches compounds that are individually known in the art for treating pain and teaches opioid antagonists such as naltrexone and opioid agonists such as morphine (Col. 27, lines 57-61). Further, it would be obvious to combine the two compositions because it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art. In re Kerkhoven, 626 F.2d 846, 205 USPQ 1069, 1072 (CCPA 1980).

Applicants further argue over the combination of Mitch with Romans, Sawynok, Frome, Fairbanks, Rueter and Mayer. Applicants assert that the combination fails to

teach the claimed invention and that it fails to provide for alleviating neuropathic pain with a composition comprising both an opioid agonist and antagonist. As explained in the previous Office Action, each type of compound listed in claims 22-34, in addition to opioid antagonists and agonists, is taught for the treatment of allodynia which is a form of neuropathic pain. It is prima facie obvious to combine compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art. In re Kerkhoven, 626 F.2d 846, 205 USPQ 1069, 1072 (CCPA 1980).

Applicants assert that because the art does not teach administering a composition comprising an opioid antagonist in an amount to enhance the pain-alleviating potency of an opioid agonist, it would not be obvious to administer a compound via the routes described in Goodman and Gilman's. The Examiner has argued the art rejections above and maintains rejections showing that the claimed invention is anticipated and also obvious. Therefore, it would be obvious to administer the compounds via different routes as taught in Goodman and Gilman's.

Applicant's amendments to the claims have necessitated the following new and modified grounds of rejection.

Claim Rejections – 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4, 6, 8, 36, 37, 41-45, 50-51, 53, 72, 80, 96-100, 106, 111 ,112, 113, 127, 133, 141, 143-145, 147, 153, 158-160 rejected under 35 U.S.C. 102(b) as being anticipated by Levine.

Levine teaches a method of treating neuropathic pain by administering nalbuphine, which is taught as a kappa-opioid agonist, combined with an opioid antagonist in a pharmaceutically acceptable carrier (meeting the limitation of claim 1; paragraphs 0003, 0010 and 0012). It is taught that nalbuphine and the opioid antagonist can be administered in the form of a pharmaceutically acceptable salt (meeting the limitation of claim 4; paragraph 0024). It is taught that the antagonist is naltrexone (meeting the limitation of claim 6; paragraph 0010). It is taught that nalbuphine is administered in a relatively low dose, which means that it is administered in a subanalgesic amount (meeting the limitation of claim 8; paragraph 0002). When the composition is used for parenteral administration, the compound is in the form of a sterile aqueous solution that may contain preservatives (meeting the limitation of claim 36; paragraph 0030). The compositions are prepared in a conventional manner by the addition of pharmaceutically acceptable ingredients including diluents (meeting the limitation of claim 37; paragraph 0031). The compositions are administered orally, intravenously, intrathecally, intramuscularly, subcutaneously and intradermally (meeting the limitations of claims 41-45 and 47; paragraphs 0028 and 0029). Claim 1 of Levine teaches that the composition is intended for a human patient (meeting the limitations of claims 49-50). Example 4 in the Levine reference teaches administration of the

combination for neuropathic pain in which the pain was not associated with the administration of a therapeutic agent (see paragraph 0052 in particular).

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4, 6, 8-10, 14, 36-38, 41, 42, 44, 45, 47, 48, 49, 50, 80, 87, 96, 97, 99, 100, 102, 103, 106, 113, 115, 119, 120, 121, 122, 123, 127, 133, 141, 143, 144, 146, 147, 149, 150, 151, 153, 160, 162, 166, 167, 168, 169 and 170 rejected under 35 U.S.C. 102(b) as being anticipated by Crain et al. (US Patent 5,580,876).

Crain et al. teach a method of administering an analgesic or sub-analgesic amount of a bimodally-acting opioid receptor agonist and an amount of an excitatory opioid receptor antagonist formulated in compositions with a pharmaceutically acceptable carrier (meeting the limitation of claims 1, 8, 133; Col. 2, lines 13-20 and Col. 5, lines 22-25). The agonists and antagonists used in the composition may be in the form of pharmaceutically acceptable acid addition salts (meeting the limitation of claim 4; Col. 5, lines 1-4). Suitable bimodally-acting opioid agonists include morphine (meeting the limitation of claims 9-10, 87; Col. 4, lines 35-36) and suitable antagonists include naltrexone (meeting the limitation of claims 6, 14, 106, 141, 153; Col. 4, lines 60-62). The composition may include additives (meeting the limitation of claim 36; Col. 5, lines 40-42), diluents (meeting the limitation of claim 37; Col. 5, lines 31-37), and binders (meeting the limitation of claim 38; Col. 5, lines 31-37). The compositions are formulated for oral (meeting the limitation of claims 41, 96, 143; Col. 5, lines 39-47),

intravenous, intramuscular and subcutaneous (meeting the limitation of claims 42-45, 97, 99, 100, 144, 146, 147; Col. 5, lines 48-58), and transdermal administration (meeting the limitations of claims 47, 48, 102, 103, 149, 150, 151; Col. 5, lines 59-65). The combination composition is intended for use in humans or animals (meeting the limitations of claims 49-50; Col. 5, lines 8-10). Crain specifically teaches that the opioid antagonist enhances the analgesic potency of the opioid agonist and attenuates antianalgesia, hyperalgesia, hyperexcitability, physical dependence and/or tolerance effects associated with the administration of the agonist (meeting the limitation of claims 80, 127, 160; Col. 2, lines 8-20). Crain teaches that the amount of the opioid antagonist is between 1,000 and about 10,000,000 fold less than the amount of the opioid agonist administered (meeting the limitations of claims 115, 119-123, 162, 166-170; Col. 6, lines 24-29).

Claim Rejections – 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6, 8-10, 14, 22-45, 47-54, 72-74, 77, 80, 83, 87, 96-100, 102-103, 106, 111-127, 130, 133, 141, 143-147, 149-151, 153 and 158-173 rejected under 35 U.S.C. 103(a) as being unpatentable over Mitch et al. (U.S. Patent 5,998,434) in view of Romans et al. (7,015,371) and Sawynok et al. (6,211,171) and Frome (2003/0060463)

and Fairbanks et al. (6,054,461) and Rueter et al. (2003/0216448) and Mayer et al. (5,502, 058).

Mitch et al. teach a method for treating pain in which it is taught that opioid antagonists and opioid agonist-antagonist combinations are useful (Col. 27, lines 54-57). Preferred opioid antagonists include naltrexone and a preferred agonist is morphine (Col. 27, lines 57-61). Mitch et al. further teach that non-steroidal anti-inflammatory drugs, including aspirin and ibuprofen, are also useful in the compositions of the invention (Col. 27, lines 23-29). It is taught that compositions of the invention are useful in the sciatic nerve ligation model, which is an animal model to treat allodynia (Col. 32, 15-35). The compositions of the invention include a colloidal dispersion system, a diluent, a binder, a plasticizer and preservatives (Col. 31, lines 40-64). The compositions can be administered orally, intravenously, intramuscularly, subcutaneously and transdermally (Col. 27, lines 14-19). The compound can be administered to mammals and humans (Col. 31, lines 54-57). It is further taught that active compounds will be administered in a dose range of 0.005 to about 500 mg/kg of body weight (Col. 27, lines 2-3).

Mitch et al. do not teach a method of treating neuropathic pain in a patient with a composition comprising gabapentin, desipramine, ketamine, anti-dynorphin antibodies, A-85380, bupivicaine hydrochloride, intrathecal administration, or daily dosage regimens.

Romans et al teach a method of treating neurogenic pain, including mechanical allodynia (Col. 7, lines 3-6) using von Frey testing for pain behavior (Col. 7, lines 35-37).

Morphine sulfate and gabapentin were tested for analgesia in mechanical allodynia and analgesia was observed after administration of morphine and gabapentin (Table 1).

Sawynok et al. teach a method of producing analgesia using tricyclic antidepressants, with desipramine being a preferred compound (Col. 9, lines 23-26, 66-67 and Col. 10, line 1). Desipramine was tested in the spinal nerve ligation model of neuropathic pain (Col. 12, lines 53-59).

Frome et al. teach a method of treating allodynia with ketamine (paragraph 0084, 0086 and 0090).

Fairbanks et al. teach that allodynia can be induced by dynorphin (Col. 3, lines 6-7); therefore it would be obvious that an anti-dynorphin antibody would be produced as an immune response to pain.

Rueter et al. teach a method for pain reduction (including allodynia; paragraph 0030, 0033). The NNR agonist A-85380 was used in a model of neuropathic pain (Example 3).

Mayer et al. teach the use of the compounds such as ketamine (Col. 3, line 39) and bupivicaine hydrochloride (Col. 6, lines 28-29) to treat neuropathic pain, which is defined as hyperalgesia or allodynia (Col. 1, lines 28-42).

Furthermore, it is obvious to vary and/or optimize the amount of naltrexone and morphine provided in the composition, according to the guidance provided by Mitch et al. and Roman et al., to provide a composition having the desired properties such as the desired concentrations of opioid antagonist and opioid agonist to effectively treat allodynia. It is also obvious to vary and/or optimize the dose of opioid antagonist that

will enhance the potency of the opioid agonist. It is also obvious to vary and/or optimize the treatment regimen of administration of the opioid antagonist or opioid antagonist-agonist combination, according to the guidance provided by Mitch et al, to provide the most efficient treatment regiment to effectively treat allodynia. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220, F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Accordingly, it would have been obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of the prior art references because each reference individually teaches the various compounds for treating allodynia, a form of neuropathic pain. It is prima facie obvious to combine compositions each of which is taught by the prior art to be useful for the same purpose (treatment of allodynia), in order to form a composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art. In re Kerkhoven, 626 F.2d 846, 205 USPQ 1069, 1072 (CCPA 1980). Furthermore, one would be motivated to combine opioid antagonists with the various compounds listed in an effort to maximally treat allodynia.

Claims 46, 101 and 148 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodman & Gilman's: The Pharmacological Approach to Therapeutics (Tenth edition, page 8).

Goodman & Gilman's teaches various common routes of drug administration therefore making it obvious to utilize any route for drug administration of the present invention (pages 5-8).

Accordingly it would have been obvious to one having ordinary skill in the art at the time of the invention to administer the claimed composition by any known route of drug adminisration as is taught ins4 Goodman & Gilman's. One would have been motivated to provide drug delivery any known form in order to achieve the most rapid effect of the drug.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Renee Claytor whose telephone number is 571-272-8394. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Renee Claytor

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER